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ABSTRACT

Objective. As recommended for subscribers to the WHO Global Health Sector Strategy on viral hepatitis, and to inform the development of a national strategic plan for Malaysia, we estimated the long-term burden incurred by the care and management of patients with hepatitis C virus (HCV) infection. We compared cumulative healthcare costs and disease burden under different treatment cascade scenarios.

Methods. We attached direct costs for management/care of chronically HCV-infected patients to a previously developed clinical disease progression model. Under assumptions regarding: disease stage-specific proportions of model-predicted HCV patients within care, annual numbers of patients initiated on antiviral treatment, and distribution of treatments over stage, we projected the healthcare costs and disease burden (in DALY) in 2018-2040 under four treatment scenarios: (a) no treatment/baseline; (b) pre-2018 standard of care (pegylated interferon/ribavirin); (c) gradual scale-up in direct-acting antiviral (DAA) treatment uptake that does not meet the WHO 2030 treatment uptake target; (d) scale-up in DAA treatment uptake that meets the WHO 2030 target.

Results. Scenario (d), while achieving the WHO 2030 target and averting 253,500 DALYs compared with the pre-2018 standard of care (b), incurred the highest direct patient costs over the period 2018-2030, of US$890 million (95% uncertainty interval: 653–1,271 million). When including screening programme costs, the total cost was estimated at US$952 million, which was 12% higher than the estimated total cost of Scenario (c).

Conclusions. The scale-up to meet the WHO 2030 target may be achievable with appropriately high governmental commitment for the expansion of HCV screening to bring sufficient undiagnosed chronically-infected persons into the treatment pathway.

Key Points for Decision-makers

- WHO initiatives to greatly reduce the burden of HCV by 2030 have led many – mostly well-resourced – countries to update national treatment policies to include the new and highly effective DAA therapies.
- For the first time, we make available projections of the direct healthcare costs of HCV management under different treatment scenarios for Malaysia.
- An enormous scale-up in screening activity and treatment uptake is needed to meet the WHO 2030 targets; due to savings in care costs this scale-up is only moderately more expensive than a less steep scale-up strategy.

1. INTRODUCTION

The World Health Organisation (WHO) Global Health Sector Strategy (GHSS) for hepatitis has set ambitious goals for reduction of the forecasted disease burden associated with chronic hepatitis C virus (HCV) infection, and eventual elimination (by 2030) [1]. In the action plan for the WHO Western Pacific Region (WPR), of which Malaysia is a participating country, plans for phased implementation of testing, treatment, and patient management services have been formulated [2], and interim targets for diagnosis of 30% of chronically-infected persons and for treatment of 50% of eligible patients were set for 2020. The corresponding WHO GHSS viral hepatitis targets for 2030 are 90% of chronically-infected persons diagnosed and 80% of eligible patients initiated on antiviral therapy, with a cure rate of 90%. The latter target depends on availability and delivery of treatment using all-oral direct-acting antivirals (DAA).

Challenges in the timely expansion of service and care provision notwithstanding, a major hurdle to meeting the WHO treatment uptake targets using highly effective DAA therapies is affordability [3,4]. In the Asian region, relatively few HCV patients have received DAA treatment to date due to barriers to accessibility (i.e., availability or cost), and to entering the care pathway [5]. In Malaysia, recent governmental developments, namely the offer of a voluntary licensing agreement and the issuing of a compulsory license for sofosbuvir, will allow acquisition of DAAs at affordable prices.

Reducing the currently high disease burden for many Asian countries is subject to numerous obstacles. To assist in national strategic planning, model-based projections of both the HCV disease burden, and the healthcare costs incurred for the management, care, and treatment of chronic HCV patients are valuable [1]. In previous work, a Markov model of the disease

progression pathway of HCV-related liver disease was developed for the Malaysian setting, and the disease burden was forecasted to the year 2039 assuming the best available standard of treatment: pegylated interferon/ribavirin (PegIFN/RBV) [6]. In the current analysis, we extend this disease burden projection model, attaching disease stage-specific healthcare costs to each patient-year and adopting the much more effective and tolerable DAA treatment, to project national-level annual HCV patient management and treatment costs.

The main objective of this paper is therefore to estimate the future (long-term, from 2018 to 2040) economic implications for the Malaysian healthcare system attributable to management of HCV patients. We compare the healthcare costs and disease burden, in disability-adjusted life-years (DALYs), under four treatment cascade scenarios: (a) no treatment; (b) pre-2018 standard of care (PegIFN/RBV antiviral treatment), (c) all oral DAA treatment, with a gradual scale-up in annual treatment uptake that would not meet the WHO 2030 target; (d) DAA treatment with a scale-up in annual uptake to meet the 2030 target. The latter two scenarios assumes that sufficient expansion of screening/diagnosis and treatment services could be achieved to meet these targets. We combined the estimated costs for the expansion of screening with direct healthcare costs to arrive at a total cost for achieving the scale-up scenarios.

2. METHODS

2.1 Model description

We calculated and attached direct patient care costs to an HCV disease progression model developed for the Malaysian setting. As in previous modelling work, clinical progression from acute HCV infection through liver-related death was simulated using an age-structured multi-

state Markov model [6]. We expanded our previous model with three additional compartments (Fig. 1). Ethical approval and informed consent were not required for this modelling study.

The model disease states are acute infection (AI), recovered (R), chronic infection (CI), moderate chronic hepatitis (MCH), compensated cirrhosis (CC), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) concurrent with CC, HCC concurrent with DC, and death from DC/HCC. MCH corresponds to Metavir stage F2-F3 (i.e., moderate/advanced fibrosis), and CC to Metavir stage F4. Two further states denote viral clearance through antiviral treatment, but without recovery from liver disease: CC-RNA– and DC-RNA–. The model parameters that describe the flow between disease states (annual transition probabilities between compartments), and excess mortality rates due to non-liver related causes were obtained from the literature (Online Resource, Table S1). Liver transplantation was not included as an additional pathway, as very few transplants are performed on HCV patients in Malaysia.

The model cycle length was set at one year, and the clinical progression of cohorts of acutely infected patients comprising 86 age-groups was modelled, from <1 year through 85 years of age. For simplicity, all simulated patients were assumed to die after age 85. The simulation start year was 1960 (i.e., HCV was assumed to circulate from 1960), and the model was run up to and including 2040. The annual number of new acute infections was simulated using separate age-distributions for people who inject drugs (PWID) and non-PWID risk groups (see Ref. 6). Assumptions regarding HCV incidence over time were also adopted from the previous study (see Online Resource).

2.2 Treatment cascade scenarios

Healthcare cost and disease burden projections will depend on the number of chronically-infected patients that are initiated on treatment. We describe each of the four scenarios explored below. For all scenarios, the historical annual numbers of patients initiated on treatment nationally were estimated based on interferon sales (R. Mohamed, pers. comm.). From these figures, an estimated 400, 450, 470, 450, 480, 645, 536, 554, 547 and 402 patients were treated from 2006 through 2015. For 2003 through 2005, 200, 300, and 350 patients were assumed to have been treated, with zero patients assumed treated prior to 2003. The estimates for 2016 and 2017 are lower, at 300 patients, as some patients were delaying treatment until the availability of DAA, patients with mild disease have been advised to continue clinical monitoring, and others have been recruited into clinical trials. All scenarios are identical up to the simulation year 2017; from 2018 differing assumptions regarding levels of treatment uptake and distribution of total treatments over disease stage influence the projections of both disease burden and annual direct costs.

Genotype distribution and SVR rates. From data on patients who received antiviral therapy at Selayang Hospital between 2000 and 2014, the assumed genotype distribution was 64% G3 and 36% G1/other [7]. Sustained virologic response (SVR) rates for interferon-based treatment of 62% for G3 and 43% for G1/Other from the Malaysian routine care setting were adopted [8]. For DAA treatment, we adopted intention-to-treat SVR rates for CI and MCH stage patients of 88% [9] and 94% [10] for G3 and G1/Other, respectively. For CC and DC stage patients, the SVR rate was set at 78% for all genotypes [11].

Scenario A. No treatment. We included this as a baseline scenario to gauge the costs of care and management of patients with HCV-related liver disease alone.

Scenario B. Pre-2018 standard of care. We defined this scenario to quantify the difference in the total cost of care and treatment using DAAs and the previous standard of care using interferon therapy. Prior to 2018, care guidelines issued by the Malaysian Ministry of Health were for interferon-based treatment; we assumed annual numbers of patients initiated on therapy at 2017 levels (i.e., 300 patients per year). In this scenario, treatment is only given to patients within the moderate chronic hepatitis and compensated cirrhosis stages.

Scenario C. DAA treatment, with gradual scale-up in treatment uptake. Starting with 1500 patients treated with DAA in 2018, this annual number was increased by 500 per year throughout the rest of the simulation period. This scenario was devised on the basis of informal estimation of the annual increase that would allow expansion of screening and treatment services.

Scenario D. DAA treatment, with treatment scaled-up to meet WHO GHSS 2030 uptake target. This scale-up to meet the WHO 2030 uptake target required a steep rise in the numbers of patients treated annually, from 5000 in 2018 climbing to 30,000 in 2025-2028, with the number decreasing to 5,000 patients per year initiated on treatment thereafter (Online Resource, Fig. S3).

For scenarios C and D only, the estimated cost of a screening programme to deliver the required annual numbers of treated chronically-infected patients [12] was incorporated to

estimate the total economic burden. This stepwise strategy uses existing screening/diagnosis efforts as a starting point, followed by prioritised targetting of active and former PWID, with intensive general population screening as a final phase.

For the scenarios involving DAA treatment (C and D), treatments were distributed over disease stage according to the distribution at initial presentation at Selayang Hospital (the national tertiary care referral centre for liver disease) [7]. Treatment was only considered viable for patients without HCC. For scenario C, treatments were distributed among untreated patients in the pre-HCC states throughout the entire simulation period as follows: CI=22%, MCH=48%, CC=26%, DC=4%. For scenario D, this distribution was used for 2018-2022; then, from 2023 onwards the anticipated effect of scaled-up screening reaching more early-stage patients was simulated by increasing the percentages of CI and MCH patients receiving treatment and reducing the percentages of CC and DC, settling on the distribution CI=53.25%, MCH=45.25%, CC=1.0%, DC=0.5% in 2037-2040 (Online Resource, Fig. S1). With respect to interferon-based therapy (scenario B; all scenarios pre-2018), treatments were distributed among pre-cirrhotic (69%; all assumed in MCH stage) and cirrhotic (31%; all CC stage) patients only; this distribution was based on Selayang Hospital data [7].

2.3 DALY computation

The composite DALY measure sums premature mortality (in years of life lost, or YLL), calculated as the number of deaths multiplied by the remaining life expectancy at age of death, and morbidity (in years lived with disability, or YLD), calculated as the number of prevalent cases multiplied by the disability weight [13]. The DALY for chronic HCV infection is therefore the sum of the YLL and YLD associated with all disease states following acute infection in the

progression model. We used the same disability weights as in the previous study [6, 14, 15], and adopted life expectancy values from the WHO Global Health Observatory [16].

2.4 Patients within care, and initiated on treatment

As direct costs are attached only to patients in care, our projections require data on the annual numbers of patients in care within each disease stage (so costs associated with medical care and management can be estimated). We assumed that only symptomatic patients are in care, and estimated that 15% of CI and MCH patients, 60% of CC stage [17] and 100% of DC and HCC stage patients are symptomatic. Of the symptomatic patients only, 10% of CI and MCH stage, and 70%, 100%, and 100% of CC, DC, and HCC stage patients, respectively, were assumed to be in care and therefore incur costs (R. Mohamed, pers. comm.).

For simplicity, we assumed that all referred patients incur antiviral treatment costs, including those that fail to start or complete treatment because of the following reasons: non-compliance/refusal, deemed unsuitable by physician, death, or loss to follow up. As the SVR rates adopted were all from intention-to-treat study designs, we do not need to separately account for patients not completing therapy when calculating treatment costs.

To achieve the high WHO treatment uptake target of 80% of all eligible chronically-infected persons in 2030 (scenario D), a corresponding steep scale-up in the annual numbers of patients entering the treatment pathway is also required. A comparable scale-up in screening/diagnosis would also be needed to ensure sufficient individuals for the next step of the cascade (referred for treatment).

2.5 Calculation of direct healthcare costs

We used the public payer perspective, and calculated healthcare costs and resource use only. As our focus was on direct patient care/management costs, we excluded programme costs for screening and testing and the indirect costs of HCV disease; however, the estimated cost of an expanded screening programme was also taken into consideration (see 3.2 below). Future costs were inflation-adjusted according to a rate of 2.5% (estimated based on recent Consumer Price Indices (CPI)). All annualized costs are those within the public healthcare system as most of HCV treatment is performed within this system, although private healthcare options do exist in Malaysia. In view of highly subsidised public healthcare and the fact that the majority of HCV infections occurs within economically-disadvantaged populations such as PWID [18], most HCV care is performed at public healthcare facilities. DAA costs were calculated based on estimated prices through competitive market pricing by government negotiations with voluntary license manufacturers for sofosbuvir and velpatasvir at RM3000 per 12-week course. Ribavirin was estimated at RM360 per week. See Online Resource for further details on costing. Given recent announcements by the Malaysian Ministry of Health (MMH) of a RM1000 price tag for generic DAA under compulsory licensing to be provided to patients at 18 MMH hospitals [19], we investigated the effect of lower DAA pricing via sensitivity analysis (see below).

2.6 Outcomes

Model outcomes, for each year of the period 2018-2040 were: (i) cumulative proportion of eligible patients who have been initiated on treatment (to evaluate WHO targets)(see Eq. 1 below); (ii) cumulative proportion of eligible patients achieving SVR (see Eq. 2); (iii) total annualised costs per disease stage; (iv) cumulative DALYs due to chronic infection; and (v)

percent reduction in annual projected deaths from DC/HCC, compared with the annual modelled deaths in baseline year 2015. We define 'eligible patients' as those who are living with chronic HCV infection. Note that the percentage of eligible patients treated required to meet the WHO WPR 2020 target of 30% of chronically-infected patients diagnosed and 50% of diagnosed patients treated, is 15%. Similarly, for the WHO 2030 target year, the 90% diagnosed and 80% treated targets correspond to 72% (0.9 x 0.8) of eligible patients.

We now describe how outcomes (i) and (ii) were calculated. The denominator of both Eq. 1 and Eq. 2, *TotalEligible,* is defined as the model-estimated number of living chronically-infected persons in the year 2015 (*n*=378,000; common to all four scenarios), and the numerator of each equation describes the cumulative number of treated patients (Eq. 1) or the cumulative number of patients achieving SVR (Eq. 2) between the year 2003 and year t.

$$CumulPropTreated_t = \frac{\sum_{2003}^{t} Treated}{TotalEligible} \quad \text{(Eq. 1)}$$

$$CumulPropSVR_t = \frac{\sum_{2003}^{t} AchievedSVR}{TotalEligible} \quad \text{(Eq. 2)}$$

Outcome (v) was included to evaluate the WHO target for a reduction in hepatitis C mortality. It is calculated simply as the projected number of deaths from DC/HCC in a given year of the simulation period, divided by the number for the year 2015 (*n*=1392).

2.7 One-way sensitivity analysis

For scenario D only, we investigated the impact on total cost (period 2018-2030) from 20% lower or higher values for parameters treated as constants: acute infection incidence from 2016, proportion of CI, MCH and CC stage patients who are symptomatic and in care. We also

calculated the total cost assuming universally lower DAA prices (i.e., available for all patients, not just for the 18 MMH hospitals), of RM1000 and a value in between, RM2000.

2.8 Simulation procedure

All model parameter values are summarised in Online Resource, Tables S1 and S2. The disease progression model was implemented and run using R version 3.2.0 [20]. Markov-chain Monte-carlo (MCMC) sampling methods in a Bayesian framework were used to propagate uncertainty in model parameters to annual costs and DALY estimates. Sampling from the posterior distributions for each parameter was carried out via MCMC simulation using OpenBUGS version 2.2.2 [21] and the BRugs package for R [22]. Two thousand MCMC samples were discarded as burn-in, with the next 2,000 samples per chain forming the posterior distributions for all parameters.

2.9 Model validation

Validation of the model using recently proposed criteria [23] was carried out by the research team consisting of a modeller/epidemiologist, two hepatologists and two health economists. Consensus on input data (costs, disease progression and other model parameters) was achieved by considering the international literature and the Malaysian context. The costing methodology, including the perspective, time horizon, and calculation approach were considered appropriate and to adhere to standard recommendations for health economic research. All costs were collected through primary data collection and reflect the financial implications of treating and managing HCV disease within the standard clinical pathway in Malaysia and recent WHO treatment guidelines. Face validity of the conceptual model, input data, and outcomes were also verified. Model code was checked for logical correctness by

assuming a fixed size cohort of chronically infected HCV patients and then enumerating the number of persons progressing to each subsequent disease stage. Validation of model outcomes using alternative input data or against empirical data could not be conducted due to a lack of suitable data.

3. RESULTS

3.1 Direct cost estimates

Table 1 shows annual direct healthcare costs per patient by disease stage, for all patients who have entered care. Costs were divided into the costs of patient management and care, and costs of treatment monitoring and drugs, with either interferon-based or DAA therapy. Values are in 2018 currency (MYR) but were converted to US dollars (at the rate of one US$ = 4 Malaysian ringgit, the approximate exchange rate on 1 January 2018) for the projections.

Annualised costs of management and care varied by disease stage due to differences in the healthcare resources used. For example, patients in the chronic infection and moderate chronic hepatitis (Metavir F0-F3) stages do not require day-care for oesophago-gastro-duodenoscopy procedures, in contrast to those patients in the CC and DC stages. Also, the type and frequency of investigations and non-HCV medication varied by disease stage.

Compared with other disease stages, HCC concurrent with DC had the highest annual treatment cost due to complex and costly clinical management required from both hepatology and hepatobiliary departments. The cost of DC alone was 31 times higher than the cost of managing pre-cirrhotic disease stages.

3.2 Cost forecasts

The annual number of patients initiated on antiviral treatment over the period 2018–2040 depends on the total number of treatments assumed, and the distribution over disease stage (Online Resource, Fig. S1). The number of patients eligible for treatment was set at the model-projected number of chronically-infected patients in 2015: *n*=378,000. The cumulative proportion of patients initiating treatment reached the WHO 2030 target (72% of total eligible patients) in scenario D only (Online Resource, Fig. S3). The treatment scale-up in this scenario was inadequate, however, to meet the WHO WPR interim target for 2020 of 15% (7.6% of total eligible patients were initiated on treatment by 2020; Table S3).

The estimated screening programme costs to deliver the needed annual numbers of chronically infected patients to be initiated on treatment for scenarios C and D are US$15 million and US$62 million [12], respectively. The higher cost for D is due to the extensive general population screening effort required.

The annual projected patient care/management costs due to chronic HCV infection in Malaysia from 2018 until 2040 are compared across scenarios in Fig. 2. Scenario D shows a peaked pattern, with annual costs rising until 2025 and then dropping thereafter, mimicking the scaling-up assumed in the annual number of patients initiated on treatment. The remaining scenarios indicate rising burden, with the lowest burden for the 'gradual DAA scale-up' (C) and 'no treatment' (A) scenarios (Table 2). Although these two scenarios had the lowest projected cumulative direct costs for the period 2018-2030, this was offset by the 26% and 37% higher cumulative DALYs projected for scenarios C and A, respectively, compared with D (Table 2).

Combining direct patient costs with screening programme costs, scenario D was 12% more expensive (US$952 million vs. US$847 million) than scenario C (Table 2).

For the gradual scale-up scenario (C), annual direct costs were projected to increase 1.4-fold by 2040, from US$51 million (95% UI:34-77) in 2018 to US$70 million (95% UI:47-113) in 2040. For scenario (D), annual direct costs increased by approximately the same factor – 1.5-fold – between 2018 and the observed peak in 2025 (i.e., a consequence of the peak annual number of treated patients, *n*=30,000, being reached in 2025). The majority of the non-treatment costs (for the period 2018-2030) in scenarios B and C was for the management and care of patients in the CC, DC and HCC states: 95.5% and 91.2%, respectively; for scenario D this was much smaller, at 63.4%, due to advanced liver disease prevented. One-way sensitivity analyses conducted for scenario D indicated that the total cost for the period 2018-2030 was most sensitive to DAA pricing (Online Resource, Fig. S4). DAA prices of RM2000 and RM1000 reduced the median total cost by 9% and 18%, respectively.

In scenarios C and D, a respective 9.5% and 38.7% of the cumulative direct healthcare costs to 2030 were for treatment. The WHO target of a 65% reduction in mortality by 2030, compared with baseline year 2015, was not achieved in any scenario (Table S3), although for scenario D this target was achieved by 2036; the annual number of end-stage liver deaths were projected to decrease from 1392 to 496 between 2015 and 2036.

4. DISCUSSION

In this study, we projected the economic implications for the Malaysian healthcare system for the care and management of patients with HCV infection, under various treatment cascade scenarios. The scenario that scaled up health service delivery to meet the WHO 2030 diagnosis and treatment uptake targets (scenario D) incurred the largest burden (in direct costs) over the period 2018-2030 – US$890 million (95% UI:653–1,270) – of which 39% was treatment-associated (including drugs) costs. This scenario also had the largest estimated impact on population health, by averting 253 thousand DALYs compared with baseline scenario (B) – the pre-2018 standard of care (Table 2). The lower direct cost of the 'gradual uptake' scenario (C) (US$832 million over 2018-2030; 95% UI:556–1,259) was offset by a substantially smaller impact on the disease burden (72 thousand DALYs averted over 2018-2030 compared with baseline scenario B). Considering patient care/management costs only, scenario D was only modestly more expensive than C, as the increased treatment costs for scenario D are almost completely compensated by the saving in care costs. This was true even when screening programme costs are additionally included; the total economic burden for scenario D was only moderately higher (12%) than for C (Table 2). This difference will diminish in the event that DAA pricing is less expensive than assumed.

Scenario D implements the projected enormous scale-up that would be required to meet the WHO 2030 treatment uptake target. We consider whether such a scale-up would be realistically achievable. Given that in many countries with high diagnosis/treatment rates, <5% of eligible patients have been initiated on treatment annually (estimates for the pre-DAA era [24]), it is unclear whether a scale-up in Malaysia from an estimated 1.1% of eligible persons in 2018 to 72% in 2030 is within the realm of possibility. In terms of annual numbers initiated on DAA therapy, Egypt – with a population three times that of Malaysia and much higher HCV

prevalence – has made remarkable progress, treating 670,000 people between Oct 2014 and Sept 2016 [25]. With the advent of DAA therapies in Australia, an estimated 30,400 to 33,400 persons were initiated on treatment between March and December 2016 [26], which suggests that the annual uptake in our scenario D could be achievable with sufficient governmental commitment and resources. Affordability of DAA would appear to no longer be a fundamental constraint, as the cumulative costs of care and treatment under DAA are highly similar to cost projections under the pre-2018 standard of care.

For Malaysia – and other middle-income countries with endemic HCV – to meet the WHO 2030 targets, or at least to reduce the disease burden to the levels projected within our 'gradual scale-up' scenario C, many barriers must be overcome. Even if available at an affordable price, highly effective antiviral treatment is insufficient unless it can be delivered to those who need it (and are aware that a cure is possible). Expansion of HCV screening, disease assessment, and treatment services may pose a greater challenge than lowering drug prices. It is notable that the assumed number of patients within care for scenario D is far lower than the number of DAA-treated patients required to meet the WHO 2030 target (Online Resource, Fig. S2).

Diagnosis of 90% of all chronically-infected persons by 2030 requires an immense case-finding effort. Well-resourced countries that have intensively attempted this task, through improvement and scaling up of ancillary and other screening programmes, have not to date managed to diagnose more than about 80% of the chronically-infected population (e.g., Australia: 82% of living infected persons were diagnosed by 2015 [27]).

In Malaysia, 28% (25,700/90,603) of HIV-infected individuals were estimated to be in treatment and care (i.e., receiving ART) in 2015 [28]. Given that HCV patients overlap substantially with HIV patients in terms of behavioural risk factors – a large proportion is PWID, who have poor access to healthcare – and may share rationale for the decision not to proceed along the healthcare pathway after receiving a positive diagnosis (e.g., not feeling unwell, difficulty in making appointments, anxiety about treatment side effects), the scaling-up of treatment uptake proposed in scenario C may be feasible. However, the estimated cumulative proportion of chronically-infected HCV patients initiated on treatment needed to meet the WHO 2030 target is 72% (achieved in scenario D only), much larger than the estimated proportion of HIV patients currently in contact with health services. This example from HIV suggests an important constraint on the expansion of HCV patient care within existing service providers: capacity needs to be greatly increased to accommodate increases in the size of the diagnosed population. The PWID population also pose challenges regarding linkage to care after diagnosis and especially with retention in care. In Australia, progression through the care cascade was historically subject to high attrition, as indicated by the small percentage (9%) of Australia's chronically-infected PWID treated by end of 2015 [29].

4.1 Limitations

To estimate the main indicators for measuring the achievement of WHO 2030 targets – the cumulative percent of patients initiated on treatment and the reduction in annual number of end-stage liver disease (ESLD) deaths – we set the baseline year to 2015 (per Ref. 1). The prevalent number of living chronically-infected persons and number of ESLD deaths in 2015 are model-based estimates, and so evaluation of target achievement depends on the validity of these figures. Finally, as there are no Malaysian incidence data, we needed to make modelling

assumptions regarding continuing transmission; thus, the expected annual growth of the HCV-infected population means that evaluation with respect to 2015 may seem overly successful.

4.2 Conclusions

In Malaysia, the economic and disease burden attributable to HCV-related liver disease is projected to increase substantially over the coming two decades. This is due, in part, to ongoing viral transmission, but the majority of the direct costs will be incurred by persons infected in the 1990s or earlier who are now progressing to advanced disease stages. Although highly effective DAA are available at affordable prices, to significantly reduce the projected disease burden, treatment annual uptake needs to be scaled up massively. To meet the WHO GHSS targets of 90% diagnosed and 80% of diagnosed patients treated by 2030, treatment uptake scale-up would have to be steeper than currently considered viable, and depends on an enormous scale-up in screening/diagnosis and the provision of treatment and follow-up services. Both direct patient care/management costs and screening programme costs are essential for comparing the total economic burden across scenarios. These projections highlight the urgent need for better HCV control/preventive measures, and for supportive policies that lead to improved case-finding and consequent referral to care and initiation on effective antiviral therapy.

Data Availability Statement. All parameter values/distributions for the natural history component, and all patient management/care and drug treatment costs for the economic component of the model are provided in the main paper and in the online resource. R/JAGS code to run each scenario can be obtained from the first author.

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Compliance with Ethical Standards. Ethical approval was not required for this modelling study. There is no source of funding to declare for this study. SAM, AA, FHS, MD, SST, AK and RM declare that they have no conflicts of interest

Author Contributions: FHS, MD and RM conceived the study. SAM implemented the HCV progression model, carried out the simulations, and drafted the manuscript. AA conducted the costing study and calculated disease-stage specific direct costs. All authors contributed to the writing of the final manuscript.

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Table 1. Direct costs for management and care (unit cost and frequencies) attached to patient-years for each of the disease states: chronic infection(CI), moderate chronic hepatitis (MCH), compensated cirrhosis (CC) (untreated), CC (RNA-ve), decompensated cirrhosis (DC) (untreated), DC (RNA-ve), and hepatocellular carcinoma (HCC), and direct costs for patients entering the treatment pathway (ie. referred for treatment: CI, MCH, CC and DC states only). All values were computed in Malaysian ringgit. Bottom rows indicate costs for patients initiated on interferon-based (scenario B) or direct-acting antiviral (DAA) (scenarios C and D) treatment.

Disease stage and cost category	***Unit cost***	***Frequency***	***Annualised cost (MYR in 2018)***
Chronic infection and moderate chronic hepatitis (Metavir F0-F3)			**906.5**
Outpatient visits	280.6	2	561.2
Investigation			345.3
Compensated cirrhosis (CC)			**1530.1**
Outpatient visits	280.6	*2*	561.2
Investigation			479.7
OGDS at daycare			489.2
Decompensated cirrhosis (DC)			**27968.2**
Outpatient visits	280.6	*4*	1122.2
Investigation (during admission and follow-up)			680.8
OGDS at day care	*489.2*	*3*	1467.8
Non-hepatitis C medication (during admission and follow-up)			13200.0
Admission		*6 (ALOS: 5 days)*	11497.6
HCC (concurrent CC)			**15533.7**
Management and care for CC			1530.0
Outpatient visits	*392.4*	*2-5*	803.1
Investigation (during admission and follow-up)			994.3
Admission		*1-3 (ALOS: 6-10 days)*	2842.5
Treatment (weightage) [TACE with DC beads (8%), TACE without DC beads (17%), RFA (23%), liver resection (7%)]			9363.8

HCC (concurrent DC)			**41971.9**
Management and care for DC			27968.2
Outpatient visits	*392.4*	*2-5*	803.1
Investigation (during admission and follow-up)			994.3
Admission		*1-3 (ALOS: 6-10 days)*	2842.5
Treatment (weightage) [TACE with DC beads (8%), TACE without DC beads (17%), RFA (23%), liver resection (7%)]			9363.8
PegIFN/RBV course, 24 or 48 weeks*			
Chronic infection and moderate chronic hepatitis (F0-F3)			19830.2 or 35382.2
Compensated cirrhosis (CC)			20009.1 or 35561.1
DAA course			
Chronic infection and moderate chronic hepatitis			4189.3
Compensated cirrhosis (CC)			4461.0
Decompensated cirrhosis (DC)			9184.6

Note. ALOS=average length of stay; TACE= Transarterial chemoembolization; DC beads=drugs that are used in chemoembolization procedure together with cytotoxic drugs that help to gradually release the cytotoxic drug to targeted cancer cells therefore preventing systemic exposure of the cytotoxic drug[3]; RFA=radiofrequency ablation. *48 weeks indicated for HCV genotype 1 patients; 24 weeks for all other genotypes. Costs were assumed identical for CC (untreated) and CC (RNA-ve) stages, and for DC (untreated) and DC (RNA-ve) stages.

Table 2. Model-projected cumulative direct costs of management and care of chronic hepatitis C virus (HCV) infected patients in Malaysia, stratified by disease state, including costs incurred by patients initiated on antiviral treatment, estimated total costs including screening programme costs, and cumulative disability-adjusted life-years (DALYs) 2018–2030, under four different treatment cascade scenarios. Cumulative direct costs are calculated for the period 2018–2030 (corresponding to the WHO Global Health Sector Strategy elimination target year). All costs are inflation-adjusted and are presented in US dollars. One US$ = 4.00 Malaysian ringgit. Cumulative costs are in millions and cumulative DALYs are in thousands. 95% uncertainty intervals are provided in parentheses.

Disease state	**Scenario A**	**Scenario B**	**Scenario C**	**Scenario D**
CI	14.5	14.5	30.6	151.1
	(12.8-16.4)	(12.7-16.4)	(28.8-32.4)	(149.3-152.8)
MCH	4.9	24.9	39.9	155.5
	(3.6-6.2)	(23.7-26.2)	(38.8-41.2)	(153.2-155.5)
CC	66.7	66.6	86.5	103.7
	(44.9-94.6)	(44.6-95.6)	(65.4-114.9)	(87.0-129.1)
DC	712.7	704.9	621.6	430.4
	(427.1-1121)	(429.4-1111)	(367.0-1015)	(218.3-788.9)
HCC	55.0	55.4	52.6	48.3
	(27.5-99.7)	(27.7-98.9)	(25.4-94.6)	(23.3-87.2)
All states: direct costs only	*853.5 (552.8-1297)*	*870.4 (567.9-1294)*	*832.3 (556.1-1259)*	*890.4 (652.7-1271)*
Total cost incl. screening	– –	– –	*847.4 (571.2-1274)*	*952.4 (714.7-1333)*
All disease states: DALYs	*946.3 (735.5-1212)*	*944.6 (734.3-1204)*	*872.7 (669.7-1130)*	*691.1 (511.2-927.7)*

Note. CI = chronic infection; MCH = moderate chronic hepatitis; DC = decompensated cirrhosis; CC = compensated cirrhosis; HCC = hepatocellular carcinoma; DALY = disability-adjusted life-year. Scenario A: baseline, no treatment from 2018; B: pre-2018 standard of care, uptake PegIFN/RBV from 2018 onwards set at estimated 2017 uptake level; C: DAA treatment; gradual scale-up in treatment

uptake; D: DAA treatment; scale-up in annual numbers initiated on treatment required to meet WHO 2030 uptake target. Estimated screening programme costs from Pharos Global Health [12].

FIGURE LEGENDS

Fig. 1 Multi-state hepatitis C virus clinical pathway model. Following successful direct-acting antiviral treatment, patients in the chronic infection (*CI)* and moderate chronic hepatitis (*MCH)* states move to the Recovered compartment; patients who achieve sustained virologic response in either the compensated cirrhosis (*CC)-untreated* or decompensated cirrhosis (*DC)-untreated* state move to the *CC-RNA–* or *DC-RNA–* state, respectively, but can still progress to hepatocellular carcinoma (*HCC*) or, for patients in the DC stage only, to end-stage liver-related death.

Fig. 2 Annual direct cost projections for the management and clinical care (excluding screening) of patients with chronic hepatitis C virus infection in Malaysia, for the period 2018–2040. Values are in US dollars (one US$ = 4.00 Malaysian ringgit) and adjusted for inflation. Four scenarios are compared: A. 'no treatment'; B. 'pre-2018 standard of care'; C. 'gradual scale-up of direct-acting antiviral (DAA) treatment uptake'; D. 'scale-up of DAA treatment uptake adequate to meet WHO 2030 uptake target'. Shaded areas indicate 95% uncertainty intervals (point estimates only shown for scenario A, which almost completely overlaps with estimates for scenario B).